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10/630,227	07/30/2003	Thomas M. DiMauro	3518.1015-000	8291

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EXAMINER	
SHAFER, SHULAMITH H	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 01/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/630,227	DIMAURO ET AL.	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *10 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-83* is/are pending in the application.

4a) Of the above claim(s) *3-13,15-33,35,52 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,14,34,36-51,53-61 and 63-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/13/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims

The Examiner prosecuting your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Shulamith H. Shafer, Art Unit 1647.

Applicant's election with traverse of Group I, claims 1-65, drawn to a method of treating an inflamed orthopedic joint in the reply filed on 14 October 2005 in response to the 9 August 2005 office action is acknowledged. In response to requirement for species election, applicant has elected: (a) High specificity antagonist – Inhibitor of TNF-α synthesis; (b) Type of joint – Knee joint; (c) Additional agent – growth factor. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 3-13, 15-33, 35, and 52 and 62 are withdrawn as being drawn to nonelected species. Claims 66-83 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1, 2, 14, 34, 36-51, 53-61 and 63-65 are under examination to the extent that they read on the elected invention.

Objections

Claims:

Claims1, 2, 14, 34, 36-51, 53-61 and 63-65 are objected to as encompassing non-elected inventions. Appropriate correction is required.

Claim 59 objected to because of the following informalities: Claim 59 is a duplicate of Claim 38. Appropriate correction is required.

Claim Rejections

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 14, 34, 36-51, 53-61 and 63-65 are rejected under 35 U.S.C., second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, the independent claim of the instant invention is drawn to a method of treating an inflamed orthopedic joint. However, the method step is directed to administering an inhibitor of TNF-α synthesis into the joint space. Thus, the method step does not match the goal set forth in the preamble, so it is unclear what the claim is directed to. Adding a phrase to the effect "such that an inflamed joint is treated" would be remedial.

Furthermore, claim 1 recites administration of an "effective amount" of a "high specificity antagonist (HAS)" in such a way as to make these relative terms which render the claim indefinite. These terms are not defined by the claim, the specification

does not provide standard definitions, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 38 and 59 recite the presence of the high specificity antagonist in the formulation of 100 mg/ml; 48 discloses that the high specificity antagonist is present in a maximum amount of 0.5 mg. In the absence of a specific recited structure, the recitation of a specific dosage is meaningless.

Claims 2, 14, 34, 36, 37, 39-51, and 53-58 and 60-65 are included in this rejection since they depend from claim 1 and do not resolve the indefiniteness issue.

35 U.S.C. § 112, First Paragraph:

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim(s) 38, 44, 46, 48 and 59 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make

or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Claim 44 is drawn to sustained release device comprising a biosensor. Claim 46 recites a sustained release device which comprises an inflammatory-responsive delivery system. The specification provides no guidance and/or direction or working examples of a sustained release device which could deliver a formulation comprising an effective amount of an inhibitor of TNF-α synthesis wherein the sustained release devise comprises a biosensor (claim 44) or wherein the sustained release device comprises an inflammatory-responsive delivery system (claim 46); the only mention of devises with such disclosed limitations are in the recitation of the claims. LaVan et al (2003, Nature Biotechnology 21:1184-1189) teach that a long-term goal of *in vivo* drug delivery is to couple smart drug delivery devices to other implants, such as biosensors. The reference teaches that a limiting step in the creation of feedback-controlled drug delivery systems has been the development of stable sensors (page 1189, column 1, 2nd paragraph). The most mature technology in development of such systems is that directed to integration of drug delivery with systems to sense blood glucose levels and release of insulin in response. La Van et al teach that "no fully automatic long-term *in vivo* system has been brought to market because of stability problems with *in vivo* glucose sensors" (page 1189, column 1, 2nd paragraph). It would require undue experimentation by the skilled artisan to determine to what inflammatory signal the delivery system would respond, to develop sensors that would recognize this signal, and to develop a drug delivery device that would integrate a stable sensor and a sustained release delivery system.

Claim 38 and 59 recite the presence of the high specificity antagonist in the formulation of 100 mg/ml; 48 discloses that the high specificity antagonist is present in a maximum amount of 0.5 mg. In the absence of a specific recited structure, the skilled artisan is unable to make the recited compound.

Due to the large quantity of experimentation necessary to identify a high specificity antagonist and an appropriate inflammatory-responsive biosensor, the lack of direction/guidance presented in the specification regarding same, the complex nature of

a drug delivery system coupled to a stable sensor, the state of the prior art which recognizes the lack of a marketable feedback-controlled drug delivery system, the unpredictability of stability of biosensor systems and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 14, 34, 37, 47, 49, 51, 54 and 56 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al (2002, J Pediatric 140:125-7) in view of Dunn (2001, EP 1 153 607). Lehman et al teach the use of thalidomide therapy for recalcitrant systemic onset juvenile arthritis. The reference teaches that the patients had arthritis in the knees (page 125, column 2, 2nd paragraph and page 126, column 1 , three lines from the bottom-bottom of page), a condition involving inflamed orthopedic joints. Lehman et al disclose that thalidomide enhances the degradation of TNF-α mRNA (page 125, column 3, last paragraph) thereby inhibiting the synthesis of TNF-α, a

proinflammatory cytokine. Lehman does not teach transcapsular administration of the formulation into the knee joint, the transcapsular administration of an inhibitor of the production of the cytokine TNF-α, the transcapsular administration of an additional therapeutic agent, the administration of a formulation of less than 1 cc, the administration of the formulation closely adjacent to the outer wall of the capsule, the administration of a growth factor in an amount effective to repair joint tissue, the administration of a formulation that includes a viscosupplement and the administration performed through a needle. Dunn (EP 1 153 607) teaches the injection of a mixture of purified growth hormone and buffer solution into the joint (abstract, page 1), to treat inflammation of a joint, and specifically discloses treatment of a knee joint (column 1, 0001, line 5-7). The reference teaches the injection of a group of agents such as anti-cytokines (column 3, 0008, lines 45-47), which would by definition include an inhibitor of TNF- α synthesis. Dunn discloses that the method may include an additional step of mixing Lidocaine (an additional therapeutic agent) with the mixture of growth hormone and buffer (Column 4, 0012, lines 11-14), that a preferred volume is generally between 0.5 to 10 milliliters (column 8, 0029, lines 39-40) and that the formulation is injected utilizing a syringe into the joint space and not directly into the bone or tissue (column 7, 0027, lines 30-32, and figure 2). The reference teaches that the invention may additionally comprise the use of a lubricant or viscosupplement such as purified hyaluronic acid or hyaluronate salt (column 9, 0032, lines 25-28). Viscosupplementation is defined as a "procedure that involves the injection of gel-like substances (hyaluronates) into a joint to supplement viscous properties of a synovial fluid" (http://arthritis.about.com/od/kneetreatments/g/viscosupplement, downloaded 12/9/05). Dunn teaches the administration of a dose of growth hormone as a means of regenerating articular cartilage in the joint, thus achieving repair of joint tissue. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the formulation comprising thalidomide taught by Lehman using the administration route taught by Dunn. The person of ordinary skill in the art would have been motivated to make that modification because the art recognizes the toxic side effects of the systemic use of thalidomide and Dunn discloses a preliminary step

involving treatment of the joint with "a group of agents such as anti-cytokines, ...so as to reduce or remove deleterious activity in the joint" (column 3, 0009, lines 38-44). The skilled artisan reasonably would have expected success because Dunn discloses the injection of growth hormone into the joint to treat joint inflammation (page 1, abstract).

Claims 36, 39-43, 45, 58, 60, 61, 63-65 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al (2002, J Pediatric 140:125-7) in view of Pike et al. (2003, US PG PUB 2003/0134792). The teachings of Lehman et al. are disclosed in detail above. Lehman et al do not disclose a formulation further comprising liposomes, a sustained, controlled release device, providing continuous release, or intermittent release, a hydrogel, a formulation administered in a volume of between 0.03 and 0.3 ml (30-300 µl), a formulation in a patch attached to an outer wall of the capsule, a formulation in a depot closely adjacent an outer wall of the capsule, the release of the antagonist by diffusion through a sustained delivery device, a polymer sustained delivery device, microspheres having a plurality of degradation rates or wherein the antagonist is released by biodegradation of a sustained delivery device. Pike et al disclose a method for treating articular cartilage disorders, such as disorders of the knee (paragraph 0059), by administering IGF-1. Pike et al teach administration of a therapeutically effective dose directly at the site with a sustained release device (paragraph 0053), which would, by definition, comprise a controlled release device providing continuous release. The reference teaches that the device may be implanted within the diseased or injured joint (paragraph 0053), which could encompass attachment to the outer wall of the capsule, or a depot closely adjacent to an outer wall of the capsule. Pike et al teach the formulation may be enclosed in a semipermeable matrix of hydrophobic polymers (paragraph 0044), which would allow for diffusion for the high specificity antagonist through a sustained delivery system (paragraph 0044). The reference teaches the use of hydrogels and microcapsules (paragraph 0044) made of different materials, which would inherently have a plurality of degradation rates and comprise a device which provides intermittent release (paragraph 0044). Pike et al also teach that sustained release forms could include a colloidal drug delivery systems such

as liposomes (paragraph 0044). Pike et al teach administration of a pharmaceutical composition in a volume ranging from 100 µl to about 5 ml (paragraph 0047). The reference also discloses the release of a therapeutically effective level of IGF-1 as the matrix degrades (paragraph 0053). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the formulation comprising thalidomide, an inhibitor of the production of the cytokine TNF-α, as taught by Lehman, by using the delivery systems disclosed by Pike et al. The person of ordinary skill in the art would have been motivated to make that modification because the art recognizes the toxic side effects of the systemic use of thalidomide and US PG PUB 2003/0134792 teaches that the pharmaceutical composition of the disclosed invention may comprise one or more other therapeutic agents including but not limited to anti-inflammatory agents (paragraph 0038). The skilled artisan reasonably would have expected success because Pike et al. teach that sustained release devices are well known in the art (paragraph 0053).

Claim 50 is rejected under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al (2002, J Pediatric 140:125-7) in view of Pike et al (2003, PG PUB US 2003/0134792) and Molloy et al. (2003, Sports Med 33:381-394). The teachings of Lehman et al. are disclosed in detail above. Lehman et al. do not teach the specific use of a formulation comprising growth factor derived from platelet concentrate. Pike et al. teach injection of growth factor into the knee. Molloy et al teach that PDGF plays a significant role in early stages of healing (page 387, Column 1, Section 1.4, paragraph 1). The reference teaches that the introduction of PDGF into the injury site of healing rabbit femur-MCL-tibia complexes increases the quality of healing (page 390, column 1, paragraph 2 and Table III). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify a formulation comprising thalidomide, as taught by Lehman by adding a growth factor such as PDGF as suggested by Pike et al. and Molloy et al. The person of ordinary skill in the art would have been motivated to make that modification because the art recognizes the toxic side effects of the systemic use of thalidomide, US PG PUB 2003/0134792 teaches that

the pharmaceutical composition of the disclosed invention may comprise one or more additional therapeutic agents including but not limited to anti-inflammatory agents or growth factors (paragraph 0038) and Molloy et al. teach that PDGF has vital functions during early and intermediate stages of healing (page 391, column 2, 2nd paragraph) . The skilled artisan reasonably would have expected success because Molloy et al. teach that growth factors have vital functions during early and intermediate stages of healing (page 391, column 2, 2nd paragraph) and Pike et al teach the pharmaceutical composition of the disclosed invention may comprise one or more other therapeutic agents including but not limited to anti-inflammatory agents (paragraph 0038) and that drug delivery devices are well known in the art (paragraph 0053).

Claims 53 and 57 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al (2002, J Pediatric 140:125-7) in view of Smith et al. (2002, PG PUB US 2002/0169162). The teachings of Lehman et al. are disclosed in detail above. Lehman does not disclose the injection of the formulation into the synovial fluid or the administration of the formulation through a drug pump. Smith et al teach an implantable sustained release device for locally administering a therapeutically effective compound to a joint (paragraph 0017), including a knee joint (paragraph 0070). The device is a mechanical one implanted intraarticularly to deliver a therapeutically effective compound within a synovial capsule of the joint (abstract). The reference teaches administration of a therapeutically effective compound to the synovial fluid of a joint (paragraph 0041). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to administer a formulation comprising thalidomide as taught by Lehman et al. using the pump device disclosed by Smith et al. The person of ordinary skill in the art would have been motivated to make that modification because the art recognizes the toxic side effects of the systemic use of thalidomide and US PG PUB 2002/0169162 teaches that the device could be used to release drugs over an extended period of time in a controlled fashion. The drugs may include anti-inflammatory drugs (paragraph 0044). The skilled artisan reasonably would have expected success because Smith et al. teach the advantages achieved by an implantable sustained

release device for locally administering a therapeutically effective compound to a joint (paragraph 0017).

Claim 55 is rejected under 35 U.S.C. 103 (a) as being unpatentable over Lehman et al (2002, J Pediatric 140:125-7) in view of Cardone et al (2003, American Family Physician, 67:2147-2152). The teachings of Lehman et al. are disclosed in detail above. Lehman does not disclose removing a portion of synovial fluid prior to administration of the antagonist. Cardone et al teach a method of removing fluid from the knee joint by aspiration (page 2147, abstract, page 2151, column 2, paragraph 2). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of administration of thalidomide as taught by Lehman et al. by aspirating fluid from the knee joint prior to administration as suggested by Cardone et al. The person of ordinary skill in the art would have been motivated to make that modification because Cardone et al teach that aspiration may be performed to aid in diagnosis and relieve discomfort. The skilled artisan reasonably would have expected success because Cardone et al. teach detailed technique for performing this procedure (entire paper).

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, Ph.D. can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

SHS

ELIZABETH KEMMERER
PRIMARY EXAMINER